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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,259	01/26/2004	Xiao-Chun (Chris) Le	033110-004	6473

21839 7590 04/10/2007

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POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,259	LE, XIAO-CHUN (CHRIS)	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,11,12,16 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 11-12, 16 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-4, 11-12, 16 and 24 are pending and under examination.

Withdrawn Rejections

In view of the amendments to the claims and applicant's arguments the following rejections in the last Office action have been withdrawn:

1. The 35 USC 112, first paragraph and second paragraph rejections.

2. The 35 USC 102 over Laing.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, first paragraph

Claims 1-4, 11-12, 16 and 24, as amended, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (NEW MATTER REJECTION).

The claimed step © of concurrent with, or subsequent to, part (b))" and steps (ii)-(iii) are not supported in the as-

filed specification. While applicant had pointed out some of the newly added claimed limitations however, the support for the above claimed limitation has not been positively pointed out. MPEP 714.02 clearly states that applicant points out where in the specification this claimed limitation appears.

Claims 1-4, 11-12, 16 and 24, as amended, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As a preliminary matter, the correct number of the published application is 20050037377('377), not 2005003737, as stated by applicant.

The specification at paragraph [0147] of the published application ('377) describes the use of instrumentation that is a laboratory built capillary electrophoresis with laser induced fluorescence polarization detection. Thus, the specification fails to provide an adequate written description of a laser-induced fluorescence polarization, which relies upon said laboratory built instrument. It does not recite how this

apparatus operates in order to concurrently or subsequently determine the method steps (i)-(iii) as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 11-12, 16 and 24, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1 and 24, as amended, are unclear as to when the "concurrent or subsequent determination of step b" is appropriately done using any of the steps (i)-(iii). Furthermore, step © iii, is repetitive as the subsequent wherein clause merely repeats said step iii.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-4, 11-12, 16 and 24, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Laing (6,331,392) in view of Le et al (6,132,968).

Laing discloses in e.g., the abstract a method for screening for bioactive compounds, in particular those that bind to RNA sequences by assessing the stability and/or the conformation of an RNA target in the presence and absence of test ligands, and identifying as a ligand any test ligand that causes a measurable change in target RNA stability and/or conformation. The effect of a ligand on target RNA stability and/or conformation is assessed by measuring the fluorescence polarization of a fluorescently labeled probe. Probes include molecules, which comprise fluorescent moieties whose measurable fluorescence properties, particularly polarization are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Probe is any molecule to which a fluorescent moiety is attached, in which one or more fluorescence properties are sensitive to the stability and/or conformation of the target RNA and/or to the binding state of the probe. Suitable probe compounds include without limitation nucleic acids, particularly oligonucleotides; small RNA-binding molecules exemplified by 2-deoxystreptamine antibiotics, which bind the Rev-responsive element in HIV RNA, or other compounds that specifically recognize the major or minor groove of RNA; and proteins, and peptides derived therefrom, that recognize particular RNA sequences or

conformations. See Fig. 1. Test ligands may be derived from large libraries of synthetic or natural compounds. For example, synthetic compound libraries are commercially available. A chemical library is available from Aldrich (Milwaukee, Wis.). See the specifics of the method in Example 1.

Laing does not disclose the use of capillary electrophoresis as recited in claim 2. However, Le discloses electrokinetic chromatography by incorporating the teachings of Hjerten at col. 18, lines 45-57:

> The specificity of the methods provided herein is further enhanced by the use of capillary electrophoresis to separate fluorescent and non-fluorescent molecular entities. Capillary electrophoresis is described by Hjerten et al., U.S. Pat. No. 5,114,551, the entire contents of which are hereby incorporated by reference. Capillary electrophoresis includes the use of capillaries which are filled either with a gel (e.g., polyacrylamide) or with buffer. The use of capillary electrophoresis in the methods of the invention provides rapid sample analysis and permits the use of small sample volumes, making it particularly useful for analyzing samples of biological interest [See, e.g., Xian et al. (1996) Proc. Natl. Acad. Sci. USA 93:86-90].

Le further discloses at col.8, lines 30-50:

> Importantly, the methods of the invention are more accurate than prior art methods since they avoid potential artifacts which are caused by chemical or enzymatic nucleic digestion. Instead, the methods of the invention limit sample manipulation to extraction of nucleic acid sequences, incubation of the extracted nucleic acid sequences with proteins which are specific for the nucleic acid modification of interest and with nucleic acid

sequence modification-specific molecules, and capillary electrophoresis.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use electrokinetic chromatography(EC) as capillary electrophoresis (CE) separation in the method of Laing as taught by Le above. Le teaches that said EC, particularly, CE is an accurate method that avoid potential artifacts caused by chemical or enzymatic nucleic digestion. One having ordinary skill in the art would have been motivated to use a capillary electrophoresis in the method of Laing for the advantages derived in said use as taught by Le above.

Applicant's arguments in the last Office action is moot in view of the new grounds of rejection, above.

Double Patenting

Claims 1-2, 11 and 16, as amended, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 6,132,968('968 Patent) in view of 6,331,392 ('392 Patent) for reasons reiterated below.

The claims and specification of the '968 Patent claims/discloses a method for quantitating at least one modification of interest in a nucleic acid sequence contained in a sample, comprising: a) providing: i) a sample suspected of containing a nucleic acid sequence comprising the at least one

modification of interest; ii) a first polypeptide sequence capable of specifically binding to the at least one modification of interest, and iii) a fluorescently labeled second polypeptide sequence capable of specifically binding to the first polypeptide sequence (step a, as claimed); b) combining the sample, the first polypeptide sequence and the fluorescently labeled second polypeptide sequence to produce a fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, (step b, as claimed) and a fluorescently labeled second polypeptide sequence:first polypeptide sequence complex; c) separating the fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, the fluorescently labeled second polypeptide sequence:first polypeptide sequence complex and the fluorescently labeled second polypeptide sequence by capillary electrophoresis; d) detecting the separated fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex by laser-induced fluorescence; and e) quantitating the separated second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, thereby quantitating the at least one modification of interest in the nucleic acid sequence. Example 1, col. 20 up to Example 6, col. 27 provides detail steps of the method and the specific probes and polypeptides used in the method. The '968 Patent does not disclose fluorescence polarization. However, the '392 patent discloses the alternativeness of fluorescence and fluorescence polarization. It further discloses that particularly polarization are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Accordingly, one would have been motivated to use fluorescence polarization in the method of the '968 Patent for the benefits derived therein as taught by the '392 Patent.

Response to Arguments

Applicants note that claims 1 and 24 have been amended to recite elements of a method of identifying a binding event that are not taught or suggested in the '968 patent. For example, the '968 patent fails to teach or suggest a method of identifying a

binding complex by: 1) determining the laser-induced fluorescence polarization of the binding complex; 2) determining the laser-induced fluorescence polarization of [the] unbound probe; and 3) comparing the result obtained in (1) with the result obtained in (2). In fact, the '968 patent does not even mention "laser-induced fluorescence polarization" let alone describe its use in the detection of a binding complex. The '392 patent fails to remedy the deficiencies of the '968 patent because it too lacks any information related to "laser-induced fluorescence polarization."

In response, attention is directed to the '392 Patent which discloses at col. 8, line 35 up to col. 9, line 50:

> Fluorescence polarization or anisotropy is a highly sensitive method for detecting RNA ligands according to the present invention. When fluorescent molecules are excited with ***plane polarized light***, they emit a majority of light in the same polarized plane, provided that the molecule remains stationary during the lifetime of the excited state (4 nanoseconds in the case of fluorescein). However, if the molecule rotates or tumbles out of the plane of the exciting polarized light during the excited state, light is emitted in a different plane from that of the initial excitation. The degree to which the fluorescence emission vector moves from, e.g., a vertical to a horizontal plane is directly related to the mobility of the fluorescently labeled molecule. That is, if the fluorescently labeled molecules are large, they move very little and the emitted light remains highly polarized with respect to the excitation plane. By contrast, if the fluorescently labeled molecules are small, they rotate or tumble faster, and the resulting emitted light is depolarized relative to the excitation plane (Lackowicz, Principles of Fluorescence

Spectroscopy, Plenum Press, NY, 1983; Methods in Fluorescence Polarization, Panvera Corp, Madison Wis.).

Polarization/anisotropy is related to the speed at which a fluorescently labeled molecule rotates, which, in turn, is related to the size (molecular volume) of the fluorescent entity. Thus, when a fluorescently labeled oligonucleotide probe, for example, binds to a target RNA, the molecular volume of the fluorescent entity increases, and the fluorescence polarization value of the sample will be higher. In this embodiment, hybridization of the probe to the target RNA is allowed to proceed in the absence and presence of test ligands (i.e., in control and test combinations, respectively), and fluorescence polarization measurements are used to quantify the level of hybridization in test and control combinations. Ligands are identified as those compounds that cause a depolarization of the test combination relative to the control combination.

The present invention encompasses the use of more than one fluorescent moiety attached to a single probe (see, e.g., FIG. 2), as well as the use of two or more probes (each having a different fluorophore) in a single reaction. In either case, the only requirement is that the different fluorescence properties of the different fluorophores should be such that their fluorescence polarization can in principle be measured simultaneously. This may be achieved, for example, by choosing fluorophores whose excitation and emission wavelength maxima do not significantly overlap.

Detection of ligands by measuring fluorescence polarization is particularly suitable for high-throughput applications. For example, two instruments exist that can measure polarization of samples present in 96-well microtiter dishes; these instruments are marketed by Panvera Corp (Madison Wis.) and Jolley Instruments (Chicago Ill.). Furthermore, the RNA target may be immobilized (either on beads or on the walls of the microtiter wells), or may be conjugated to a larger molecule in solution (such as, for example, to streptavidin via a biotin moiety attached to the target RNA), thereby enhancing differences in polarization of the fluorescent probe subsequent to ligand binding.

Thus, the claimed laser light is covered or encompassed by the polarized light used by the '392 Patent since both lights induced excitation of the fluorescent molecules. These lights produce the same results that if the fluorescently labeled molecules are large, they move very little and the emitted light remains highly polarized with respect to the excitation plane.

This is recognized by applicant at paragraph [0148] of the published application 20050037377:

> There is no fundamental difference between this apparatus and the conventional fluorescence detectors that are also capable of anisotropy measurements. The only difference is that our cuvette (flow cell) is much smaller (0.2.times.0.2 square) than commercially available cells and that our detector is capable of handling the small volumes suitable for CE separation.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
March 24, 2007